REMARKS

Following the Article 34 Amendment filed in the corresponding PCT application, claims 1-41 were pending in the application. Claims 2, 3, 11, 18-20, 22, 39, and 40 have been cancelled. New claims 42-49 have been added. Claims 1, 4-10, 12-17, 21, 24, 25, 27-31, 33-35, 38, and 41 have been amended. Accordingly, upon entry of the foregoing Preliminary Amendment, claims 1, 4-10, 12-17, 21, 23-38, and 41-49 will be pending in the application. In addition, the specification has been amended to include priority information.

Support for the amendments to claims 1, 4-10, 12, 23, 25, 27, 28 and new claim 43 can be found throughout the specification, including at least at page 5, line 9 and at page 37, lines 15-17. Support for the amendment to claims 1, 5, and 41 and new claims 43, 44, and 49 can be found throughout the specification, including at page 13, line 21 and at page 35, lines 20-21. Additional support for the amendments to claim 1 and new claim 49 can be found at page 38, line 28 of the specification. Further support for the amendment to claims 1 and new claims 43 and 44 can be found at page 36, lines 30-31 of the specification. Support for the amendments to claims 21, 28, and 30 can be found throughout the specification, including at page 16, lines 28-29.

The foregoing amendments introduce no new matter and are not related to issues of patentability. Entry of the foregoing Preliminary Amendment is respectfully in order and requested. In addition, the foregoing claim amendments and cancellations have been made solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Applicants respectfully submit that the above-identified application is in condition for allowance. If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call Applicant's Attorney at (617) 227-7400.

Respectfully submitted,

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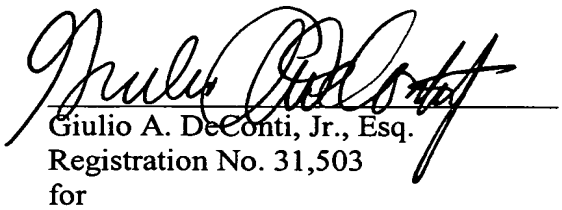

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AMENDED CLAIMS

1. An isolated and recombinant fusion peptabody, which binds to the epidermal growth factor receptor ErbB-1, ErbB-3 or ErbB-4, comprising:

(a) a portion of a humanized cartilage oligomer matrix polypeptide;
(b) an enhancer sequence located at the N terminus of the portion of the humanized cartilage oligomer matrix polypeptide;
(c) a portion of a hinge region of an immunoglobulin polypeptide located at the C terminus of the portion of the humanized cartilage oligomer matrix polypeptide;
(d) an epidermal growth factor receptor ligand located at the C terminus of the hinge region, comprising at least a motif having a three-dimensional structure, and whereby said isolated and recombinant fusion peptabody is capable of inducing cellular death in a cell expressing epidermal growth factor receptor.

2. The isolated and recombinant fusion peptabody of claim 1, wherein the member of the epidermal growth factor receptor is ErbB-1.

3. The isolated and recombinant fusion peptabody of claims 1-2, which is fully human or humanized.

4. The isolated and recombinant fusion peptabody of claims 1-3, wherein said isolated and recombinant fusion peptabody is multimeric.

5. The isolated and recombinant fusion peptabody of claims 1-4, wherein the enhancer sequence is selected from the group comprising: YSFE, YSFEDL, YSFEDLY, YSFEDLYR and YSFEDLYRR.

6. The isolated and recombinant fusion peptabody of claims 1-5, wherein said epidermal growth factor receptor ligand is selected among the group of:
(a) an epidermal growth factor polypeptide or fragments or variants thereof,
(b) a growth blocking peptide or fragments or variants thereof,
(c) a TGF alpha polypeptide or fragments or variants thereof,
(d) a plasmocyte spreading peptide or fragments or variants thereof,

(e) a paralytic peptide or fragments or variants thereof,

(f) a cardioactive peptide or fragments or variants thereof,

(g) an amphiregulin polypeptide or fragments or variants thereof,

(h) a heparin-binding epidermal growth factor-like polypeptide or fragments or variants thereof,

(i) a betacellulin polypeptide or fragments or variants thereof, or

(j) a viral EGF-like polypeptide or fragments or variants thereof.

7. The isolated and recombinant fusion peptabody of claim 6, wherein said epidermal growth factor receptor ligand is present in its full-length sequences.

8. The isolated and recombinant fusion peptabody of claims 1-7, further comprising a polyhistidine tag sequence.

9. The isolated and recombinant fusion peptabody of claims 1-8, further comprising at least one effector region.

10. The isolated and recombinant fusion peptabody of claim 9, wherein the effector region comprises a cytotoxin.

11. The isolated and recombinant fusion peptabody of claim 9, wherein the effector region comprises a detection moiety.

12. The isolated and recombinant fusion peptabody of claim 11, wherein said detection moiety is fluorescent.

13. An isolated and purified DNA sequence encoding the isolated and recombinant fusion peptabody of any one of claims 1-9.

14. A vector comprising at least one copy of the isolated and purified DNA sequence of claim 13.

15. The vector of claim 14, further comprising a promoter operably linked to said isolated and purified DNA molecule.

16. A prokaryotic or eukaryotic host cell capable of expressing the isolated and purified DNA molecule of claim 13.

17. A pharmaceutical composition comprising as an active substance a pharmaceutically effective amount of an isolated and recombinant fusion peptabody of claims 1-12 optionally in combination with pharmaceutically acceptable carriers, diluents and adjuvants.

18. Use of the pharmaceutical composition of claim17, for the preparation of a medicament for the treatment or prevention of cancer.

19. Use according to claim 18, wherein the cancer is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, liposarcoma, neuroendocrine tumor, mesothelioma, schwanoma, meningioma, adenocarcinoma, melanoma, leukemia, lymphoid malignancy, squamous cell cancer, epithelial squamous cell cancer, lung cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, testicular cancer, esophageal cancer, a tumor of the biliary tract, and head and neck cancer.

20. Use according to claim 19, wherein the cancer is head cancer, neck cancer, bladder cancer or melanoma.

21. A method of treating or preventing cancer that expresses epidermal growth factor receptors selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, liposarcoma, neuroendocrine tumor, mesothelioma, schwanoma, meningioma, adenocarcinoma, melanoma, leukemia, lymphoid malignancy, squamous cell cancer, epithelial squamous cell cancer, lung cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer,

gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, testicular cancer, esophagael cancer, a tumor of the biliary tract, and head and neck cancer, comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 17 to a subject.

22. The method of claim 21, wherein the cancer is head cancer, neck cancer, bladder cancer or melanoma.

23. A method for inducing apoptosis and/or necrosis, comprising contacting a cell with the isolated and recombinant fusion peptabody of claims 1-12.

24. The method of claim 23, wherein said cell is a cancer cell.

25. A method for inhibiting cell proliferation, comprising contacting a cell with the isolated and recombinant fusion peptabody of claims 1-12.

26. The method of claim 25, wherein said cell is a cancer cell.

27. A method of diagnosing cancer, comprising administering to a subject the isolated and recombinant fusion peptabody of claims 11-12, optionally in combination with pharmaceutically acceptable carriers, diluents and adjuvants.

28. A kit for treating cancer that expresses epidermal growth factor receptors in a human patient, said kit comprising the isolated and recombinant fusion peptabody of claims 1-12, optionally with reagents and/or instructions for use.

29. The kit of claim 28, further comprising a separate pharmaceutical dosage form comprising an additional anti-cancer agent selected from the group consisting of chemotherapeutic agents, anti-epidermal growth factor receptors antibodies, radioimmunotherapeutic agents, and combinations thereof.

30. A kit for diagnosing cancer that expresses epidermal growth factor receptors in a human patient, said kit comprising the isolated and recombinant fusion peptabody of claims 11-12, optionally with reagents and/or instructions for use.

31. A method for producing the isolated and recombinant fusion peptabody of claims 1-12, comprising the steps of:

a) constructing an isolated and purified DNA molecule encoding the isolated and recombinant fusion peptabody of any one of claims 1-12,

b) allowing expression of said isolated and purified DNA molecule in a cell system under suitable conditions,

c) recovering the isolated and recombinant fusion peptabody.

32. The method of claim 31, characterized in that the cell expression system is a prokaryotic cell.

33. The method of claims 31-32, characterized in that the suitable conditions consist in culturing the cell expression system at a temperature between 10-40 °C during 2-40 hours.

34. The method of claim 33, characterized in that the suitable conditions consist in a temperature of 37°C during 8-16 hours.

35. The method of claims 31-34, characterized in that step c) is achieved by extraction of said isolated and recombinant fusion peptabody from the cell expression system subsequently followed by purification and refolding steps.

36. The method of claim 35, characterized in that the purification is carried out in the presence of reducing agents and results in the elimination of contamination.

37. The method of claim 35, characterized in that the refolding step is carried out by direct dilution in refolding buffer and further comprises serial dialysis.

38. The method of claim 37, characterized in that the direct dilution in refolding buffer leads to a final concentration of the isolated and recombinant fusion peptabody below 300 nM.

39. The method of claim 37, characterized in that the serial dialysis comprise at least 2 different dialysis buffers.

40. The method of claim 37, characterized in that the refolding step consists in the oxidation of the isolated and recombinant fusion peptabody before its concentration.

41. A purified and isolated enhancer sequence having protein production increasing activity, characterized in that said purified and isolated enhancer sequence is selected from the group comprising: YSFE, YSFEDL, YSFEDLY, YSFEDLYR and YSFEDLYRR, a molecular chimera thereof and variants thereof.